Striatal atrophy and dendritic alterations in a knock-in mouse model of Huntington's disease.

Journal: Brain Res Bull

Publication Year: 2012

Authors: Renata P Lerner, Luz Del Carmen G Trejo Martinez, Chunni Zhu, Marie-Francoise Chesselet, Miriam A Hickey

PubMed link: 22326483

Funding Grants: SFSU Bridges to Stem Cell Research

Public Summary:
Huntington's disease (HD) is a progressive neurodegenerative disease characterized by progressive atrophy of the striatum, cerebral cortex, and white matter tracks. Major pathological hallmarks of HD include neuronal loss, primarily in the striatum, and dendritic anomalies in surviving striatal neurons. Although many mouse models of HD have been generated, their success at reproducing all pathological features of the disease is not fully known. Previously, we demonstrated extensive striatal neuronal loss and striatal atrophy at 20-26 months of age in a knock-in (KI) mouse model of HD. To further investigate this model, which carries a human exon 1 with ~119 CAG repeats inserted into the mouse gene (initially 140 repeats), we have examined whether these mice exhibit the atrophy and neuronal anomalies characteristic of HD. Stereological analyses revealed no changes in the striatal volume of male and female homozygote mice at 4 months, however striatal atrophy was already present at 12 months in both sexes. Analysis of cortical and corpus callosum volume in male homozygotes revealed a loss in corpus callosum volume by 20-26 months. At this later age, the surviving striatal neurons displayed extensive loss of spines in distal branch orders that affected both immature and mature spines. Mirroring late stage HD striatal neuronal morphology, the striatal neurons at this late age also showed reduced dendritic complexity, as revealed by Sholl analysis. Tyrosine hydroxylase immunoreactivity was also decreased in the striatum of 20-26 month old KI mice, suggesting an alteration in striatal inputs. These data further indicate that CAG140 homozygote KI mice exhibit HD-like pathological features and are a useful model to test the effects of early and/or sustained administration of novel neuroprotective treatments.

Scientific Abstract:
Huntington's disease (HD) is a progressive neurodegenerative disease characterized by progressive atrophy of the striatum, cerebral cortex, and white matter tracks. Major pathological hallmarks of HD include neuronal loss, primarily in the striatum, and dendritic anomalies in surviving striatal neurons. Although many mouse models of HD have been generated, their success at reproducing all pathological features of the disease is not fully known. Previously, we demonstrated extensive striatal neuronal loss and striatal atrophy at 20-26 months of age in a knock-in (KI) mouse model of HD. To further investigate this model, which carries a human exon 1 with approximately 119 CAG repeats inserted into the mouse gene (initially 140 repeats), we have examined whether these mice exhibit the atrophy and neuronal anomalies characteristic of HD. Stereological analyses revealed no changes in the striatal volume of male and female homozygote mice at 4 months, however striatal atrophy was already present at 12 months in both sexes. Analysis of cortical and corpus callosum volume in male homozygotes revealed a loss in corpus callosum volume by 20-26 months. At this later age, the surviving striatal neurons displayed extensive loss of spines in distal branch orders that affected both immature and mature spines. Mirroring late stage HD striatal neuronal morphology, the striatal neurons at this late age also showed reduced dendritic complexity, as revealed by Sholl analysis. Tyrosine hydroxylase immunoreactivity was also decreased in the striatum of 20-26 month old KI mice, suggesting an alteration in striatal inputs. These data further indicate that CAG140 homozygote KI mice exhibit HD-like pathological features and are a useful model to test the effects of early and/or sustained administration of novel neuroprotective treatments.